Enclosures:

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TUESDAY, MARCH 23, 2004

Worthy of Western Pennsylvania
4 sections • 40 pages

5

Antidepressants may have suicide risks

FDA urges drugmakers to place warnings on medications.

BY THE WASHINGTON POST

WASHINGTON — The federal Food and Drug Administration urged drug makers Monday to put new warning labels on popular antidepressant medications, including Paxil, Zoloft and Luvox, alerting doctors and consumers to watch for suicidal tendencies, hostility and agitation in patients taking the drugs.

The agency's action focuses on 10 anti-depressant drugs in all and follows a warning by the British government last year advising physicians not to prescribe most widely used antidepressants to children. Last month, families of American adolescents who killed themselves while taking the medications implored the FDA to take comparable steps, and an expert advisory committee urged greater vigilance in the use of the medications in children with depression.

The agency said it does not know whether the medications — which include several drugs known as selective serotonin reuptake inhibitors, or SSRIs — are responsible for reported side effects such as inner restlessness, agitation and suicidal thoughts in some people. Officials said they are drawing greater attention to known cautionary information while a team of outside researchers completes a comprehensive analysis of the possible risks.

Patients taking the drugs who experience behavioral side effects should contact their physicians, said Russell Katz, director of neuropharmacological drug products at the FDA. If the symptoms are new or severe, he added, doctors should consider lowering the dose or stopping the drug.

Yesterday's move by the agency calls for warning-label changes for adults as well as children, and for patients who are depressed as well as those who use the drugs for unrelated problems.

"The advice applies across the board whether the drugs are used for any indication — psychiatric or not," Katz said.

Critics of the medications called yesterday's move a victory and demanded that the FDA go further. Although Prozac is the only one of this class of drugs that has been specifically approved to treat depression in children, doctors are writing tens of thousands of prescriptions for many of the others, based on their clinical judgment that the drugs are safe and effective.

"Doctors are going to be on the line not to prescribe them as if they were pacifiers," said Vera Hassner Sharav, president of the Alliance for Human Research Protection, a patient advocacy group based in New York.

Many critics complain that a majority of studies of the drugs in children found the medications did no better than dummy pills in treating depression, but that these studies have been hidden from doctors and the public. The companies say the studies are proprietary.

Sharav and other critics charge that the FDA and the American psychiatric establishment, which has broadly supported the efficacy of the drugs, have been unduly influenced by the pharmaceutical industry. Dozens of lawsuits against the medications have been filed.

Many psychiatrists say the medications save lives and warn that discouraging patients from taking them could lead to greater numbers of suicides. They say suicidal tendencies or attempts among patients taking the drugs are the result of underlying disorders, not the medications.

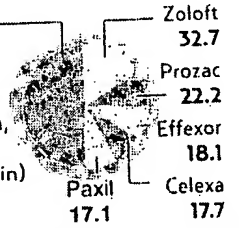
The drugs affected by yesterday's announcement are Prozac, Zoloft, Paxil, Luvox, Celexa, Lexapro, Wellbutrin, Effexor, Serzone and Remeron.

Antidepressants, use with caution

The Food and Drug Administration recommends that certain antidepressants include a warning for worsening depression or suicidal thoughts. There were over 213 million dispensed prescriptions for antidepressants in 2003.

Dispensed prescriptions for antidepressants, 2003

in millions



SOURCE: IMS Health AP

Pittsburgh Post-Gazette

ONE OF AMERICA'S GREAT NEWSPAPERS

50 CENTS THURSDAY, DECEMBER 14, 2006 VOL. 80, NO. 136 12/14/06 • FINAL

FDA may expand alert on drugs for depression

By Shankar Vedantam
The Washington Post

WASHINGTON -- Widely used antidepressants double the risk of suicidal behavior in young adults, from around 3 cases per 1,000 to 7 cases per 1,000, according to a huge federal analysis of hundreds of clinical trials. It marks the first time that regulators have acknowledged that the drugs can trigger suicidal behavior among patients older than 18.

Food and Drug Administration officials yesterday said the higher risk was found in patients between 18 and 25, and that the risk faded among older patients. The finding comes two years after the agency ordered a "black box" warning on the drug labels following discovery of a heightened risk of suicidal behavior among children taking the pills.

After reviewing the latest data, an expert federal panel yesterday recommended that agency officials tell doctors and the public of the risk, but also find a way to note that the risk declines with age — and that leaving depression untreated is also risky.

While the studies on the relationship between the drugs and suicide appear contradictory, the experts said one possibility is that the drugs may pose a risk early in treatment, but have a protective effect in the long term.

The agency is leaning toward expanding its black box warning, said Thomas Laughren, director of FDA's division of psychiatric drug products. Officials said they will try to craft language that would urge clinicians to use the drugs carefully, not abandon them.

The new finding created a dilemma for the regulators. Even as it vindicated some of what critics of drugs such as Prozac, Paxil and Zoloft have said for years, the earlier official

SEE FDA, PAGE A-6

FDA may expand alert on drugs for depression

FDA, FROM PAGE A-1

warnings about the drugs appear to have led to a drop in their use -- and there are troubling signs that this, too, can lead to an increase in suicides.

After concerns were raised in the Netherlands about the suicide risk, there was a 22 percent drop from 2003 to 2005 in antidepressant prescriptions for patients below 18, and a 50 percent increase in suicides, University of Illinois psychiatry professor Robert Gibbons said. The number of suicides went from 34 to 51.

"What we are seeing is the early signs of an epidemic of suicide in children who are no longer being treated for their depression," Mr. Gibbons said in an interview. U.S. suicide data for 2005 is not yet available, but Mr. Gibbons said the FDA's black box warning had caused a similar decline in prescriptions among children in this country. He predicted dozens of additional suicides as a result, and warned that any expansion of the black box would have a similar impact on adults.

Robert Temple, director of FDA's Office of Medical Policy, said regulators were in a bind. On the one hand, they need to tell physicians about the new results to warn them to monitor patients closely for suicidal behavior, but if that means doctors stop prescribing the drugs altogether, "I don't know what you are supposed to do."

Emotions ran high at the meeting yesterday of expert advisers, with both advocates for the drugs and their critics warning the federal regulators that a wrong move would cost lives.

Critics of the drugs said they were deeply distrustful of both the medical profession and the FDA itself because of conflicts of interest with the pharmaceutical industry. Allen Jones, of the consumer advocacy group Alliance for Human Research Protection, said, "The love affair between the pharmaceutical industry and our government institutions has to end."

Gwen Olsen, a former pharmaceutical industry representative, told the panel that she had influenced doctors by offering them free food, gifts and gimmicks to gain access to them, and then presented them with skillfully manipulated data.

Ms. Olsen said she had a change of heart after her 20-year-old niece committed suicide following a withdrawal reaction from the antidepressant Paxil. She said her niece first tried to hang herself from a ceiling fan. When the fan broke, Ms. Olsen said, she doused herself in oil and set herself alight.

Two experts critical of the drugs, British psychiatrist David Healy and Joseph Glenmullen, a psychiatrist who lectures at Harvard, said the FDA analysis played down the magnitude of the suicide risk. Information uncovered in lawsuits, they said, suggested that several suicides in industry trials were never disclosed.

"Industry controls the data, and industry, with the aid of FDA, have miscoded the data, so all the articles in all the journals that purport to represent clinical trial data are misleading," Dr. Healy said in an interview. His own analysis, published in the British Medical Journal in 2005, found a twofold increase in risk among all adults taking the drugs. "The idea you would have a risk in one age group but not another is just wrong," he said.

Other medical experts and patient advocates warned, however, that black box warnings could scare away patients from necessary treatment.

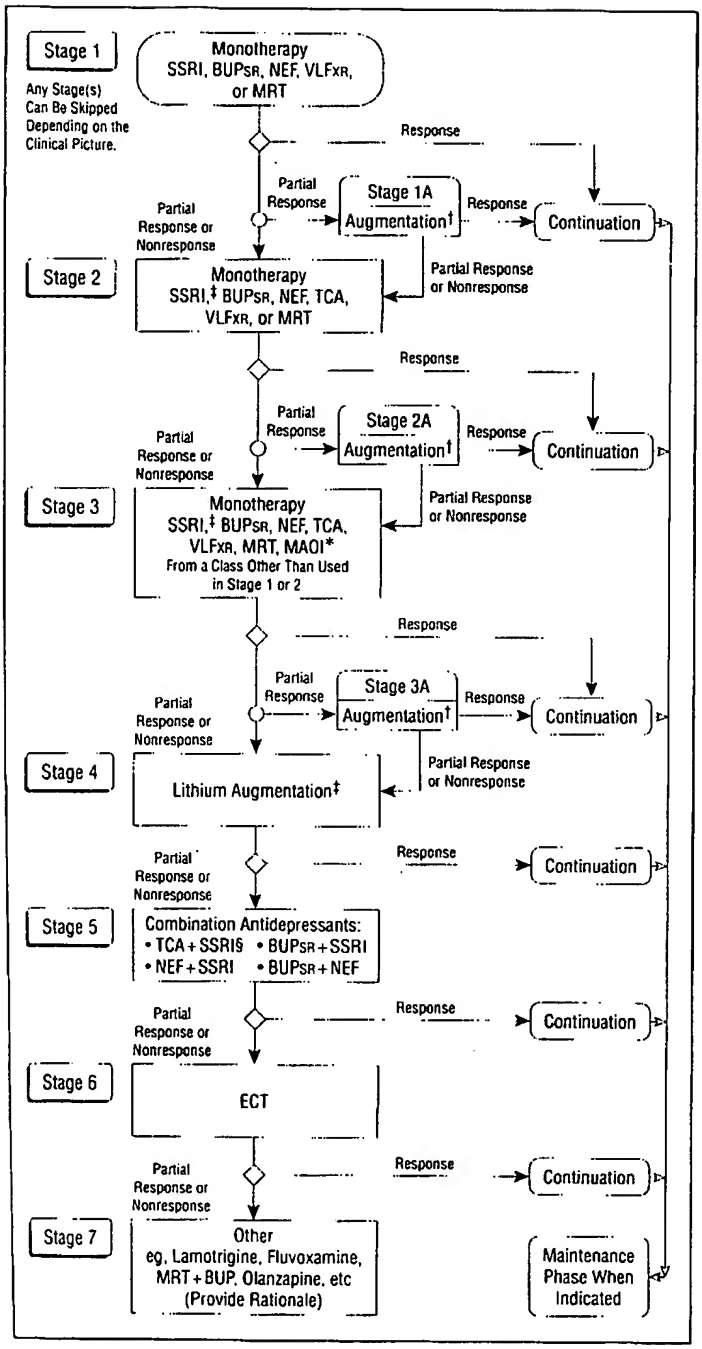


Figure 1. Strategies for the treatment of nonpsychotic major depressive disorder. Asterisk indicates consider TCA/VLF if not tried; dagger, lithium, thyroid, buspirone; double dagger, skip if lithium augmentation has already failed; section mark, most studied combination. BUP_{SR} indicates bupropion sustained release; cital, citalopram; fluox, fluoxetine; MAOI, monoamine oxidase inhibitor; MRT, mirtazapine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; VLF_{XR}, venlafaxine extended release. This figure is published with permission from the Texas Department of Mental Health and Mental Retardation and is part of a state-funded project.

Texas Algorithm July 2004 Arch Gen Psych p671

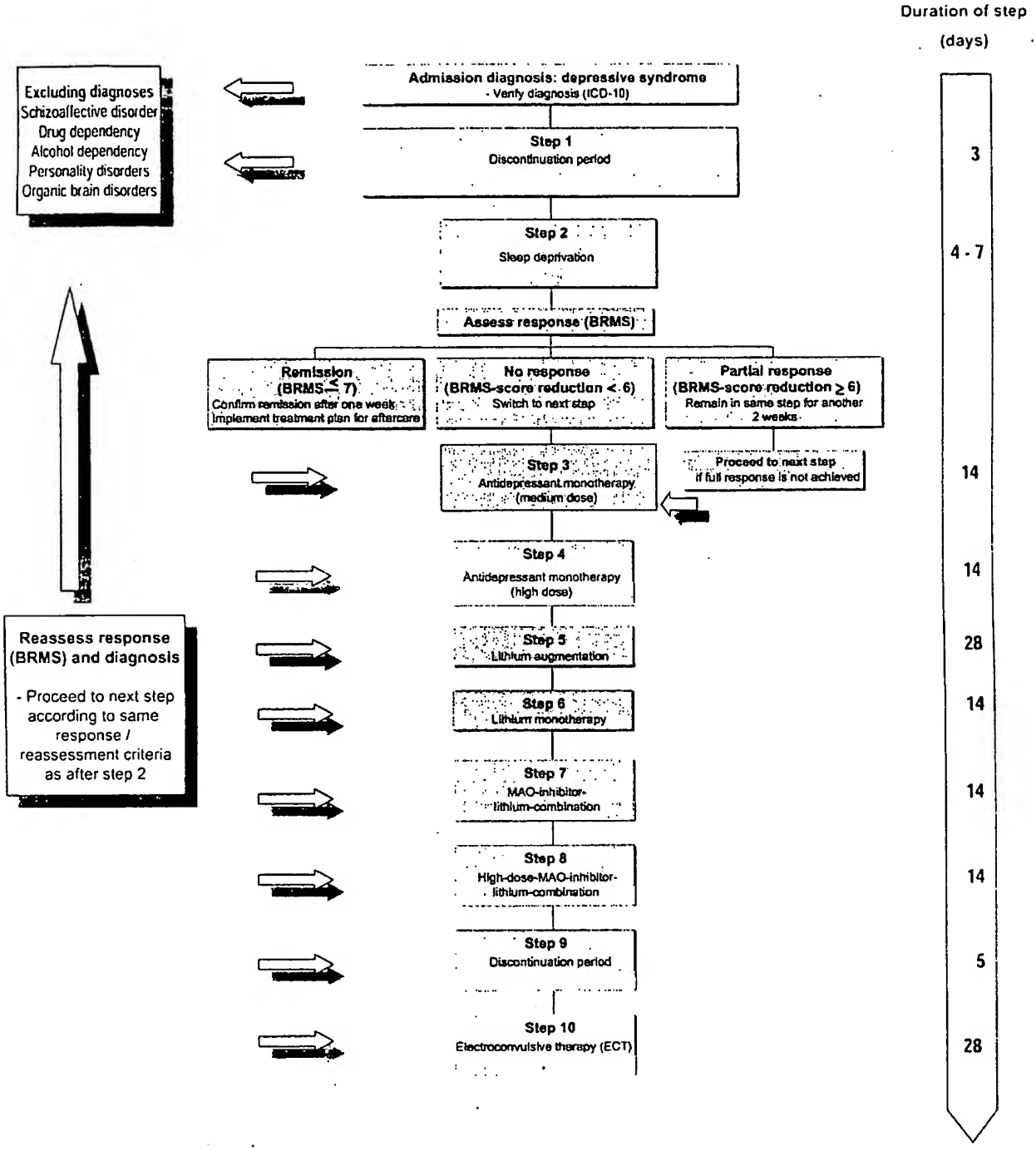


Fig. 1 The Berlin Algorithm Project, Phase 2: randomised controlled clinical trial comparing a standardized sequential drug treatment regimen (SSTR) with treatment as usual (TAU) and algorithm-guided decision making (BRMS = Bech-Rafaelsen-Melancholia-Scale; MAO = monoamine-oxidase)

Berlin Algorithm Project -in Aldi 2003

Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

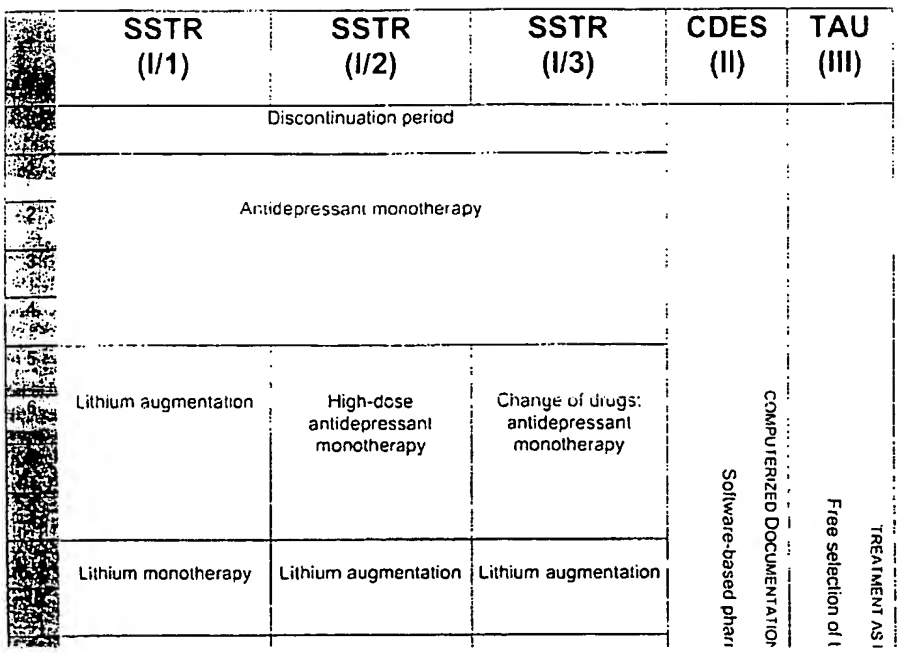


Fig. 2 The Algorithm Study of the German Research Network on Depression (SSTR = standardized stepwise drug treatment regimen, CDES = computerized documentation and expert system, TAU = treatment as usual, MAO = monoamine-oxidase inhibitor, ECT = electroconvulsive treatment, T3 = trijodthyronine)

Algorithm Study of the German Research Network on Depression -in Aldi 2003Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (www.star-d.org), a NIMH-funded, multisite clinical trial is currently underway in the United States. STAR*D prospectively evaluates stepwise treatment procedures in depression

STAR*D -NIMH funded -in Aldi 2003
Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

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enclosures from PDR (separately attached as photocopies)

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enclosure on antidepressant market (a):

The annual US antidepressant sale is $13.2 Billion. (Please see table below.)
The total antidepressant revenue worldwide was USD 17.1 billion in 2002. Another source listed that the global antidepressant market is unevenly distributed, North America accounting for about 73% of the global market, Europe representing 20%.

Another article reports (at http://www.hscareers.com/news/articles.asp?id=152), that the antidepressant drug sales are expected to *reach $20.5 Billion* by 2007, and that the number of people affected by major depression will continue to grow exponentially. This is in accordance with the academic publications noting that the rate of depression is increasing.

BEST AVAILABLE

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Home > News and Trends > Antidepressant Drug Sales Expected to Reach $20.5B By 2007

News and Trends - Antidepressant Drug Sales Expected to Reach $20.5B By 2007

PR Newswire

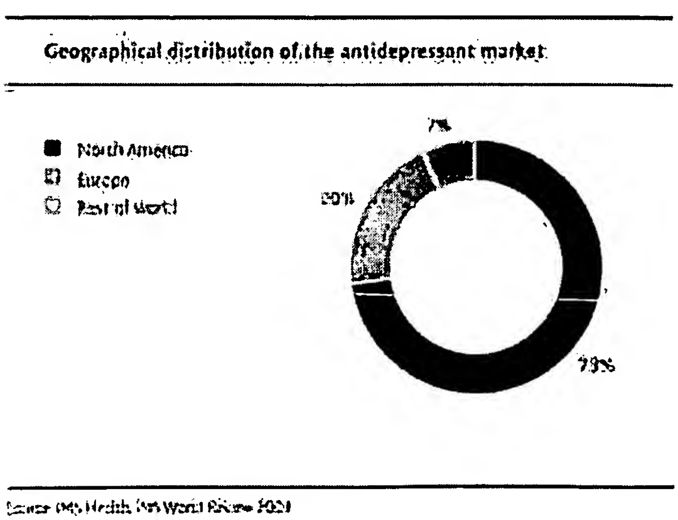
Saturday, August 03, 2002

Antidepressant Drug Sales Expected to Reach $20.5B By 2007-More Than 85% of the Drugs Researched Are Projected to Come to Market, In the U.S. And Europe, by 2007 PR Newswire - August 01, 2002

FOSTER CITY, Calif., Aug 1, 2002 /PRNewswire via COMTEX/ -- Front Line Strategic Consulting, Inc., a leader in consulting and market research for the Life Sciences industries, today announced a new Strategic Market Report(TM) Antidepressants, a Strategic Business Outlook and Market Analysis of the U.S. and worldwide. Front Line's market report provides in-depth analysis of market economics and business developments in the current and future antidepressants therapeutic market. The worldwide market for antidepressant drug sales is currently expected to reach $20.5B by 2007 due in part to unmet medical needs, technology improvements and product life extensions. Worldwide the antidepressants market will see a 3.4% compound annual growth rate from 2002 to 2007 in the development and increased availability of drugs available to combat the disease that affects over 330 million people.

"Our findings show that the number of people affected by major depression will continue to grow exponentially. This report provides companies with critical market information and a roadmap for emerging developments and strategic recommendations," said Molly Varnau, director of strategic market reports, Front Line Strategic Consulting, Inc.

... depression) is the leading cause of disability in the United ... more than two times as

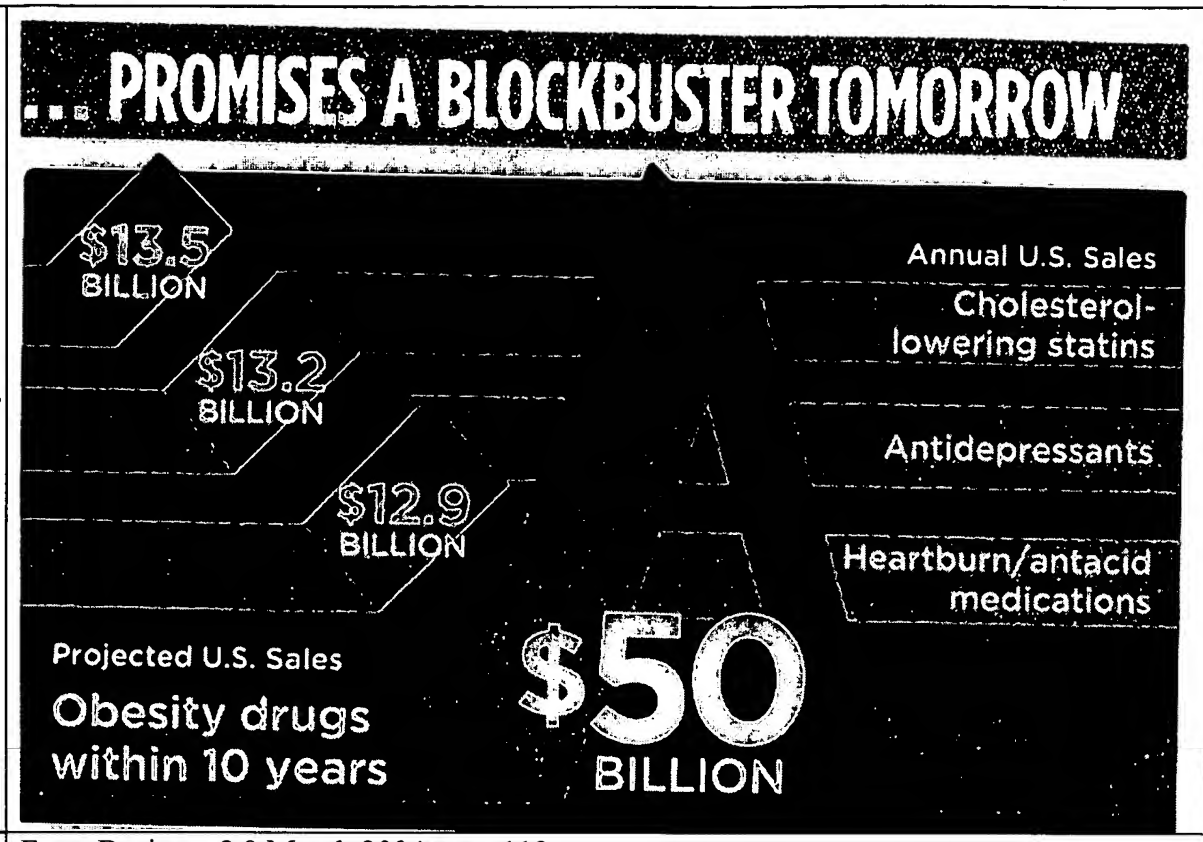


enclosure on antidepressant market (b):

Prozac was generating a billion dollar a year by some reports, and an academic publication reported that there is at least $100 Million per every percentage point gain in the antidepressant market. (Thase, 2002, (a),).

Thase, M. (2002 a): Comparing the methods used to compare antidepressants. Psychopharmacology Bulletin: Spring 2002-Vol. 36, Suppl.1 4-17

enclosure on antidepressant market (c):



From Business 2.0 March 2004 page 113

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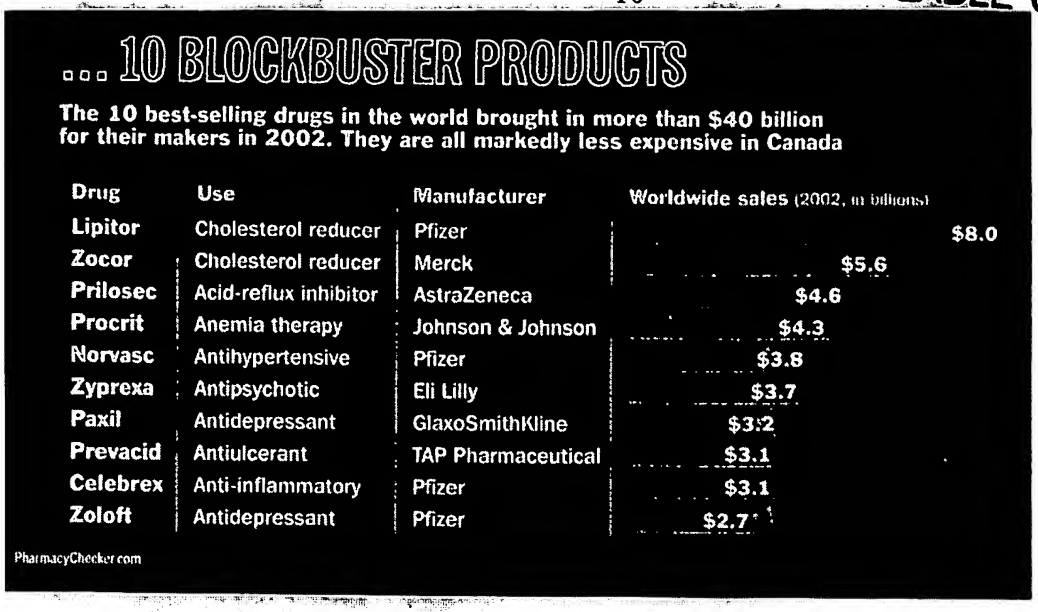
enclosure on antipsychotic market (varies by year):
see drug line 6



... 10 BLOCKBUSTER PRODUCTS

The 10 best-selling drugs in the world brought in more than $40 billion for their makers in 2002. They are all markedly less expensive in Canada

Drug	Use	Manufacturer	Worldwide sales (2002, in billions)
Lipitor	Cholesterol reducer	Pfizer	$8.0
Zocor	Cholesterol reducer	Merck	$5.6
Prilosec	Acid-reflux inhibitor	AstraZeneca	$4.6
Procrit	Anemia therapy	Johnson & Johnson	$4.3
Norvasc	Antihypertensive	Pfizer	$3.8
Zyprexa	Antipsychotic	Eli Lilly	$3.7
Paxil	Antidepressant	GlaxoSmithKline	$3.2
Prevacid	Antiulcerant	TAP Pharmaceutical	$3.1
Celebrex	Anti-inflammatory	Pfizer	$3.1
Zoloft	Antidepressant	Pfizer	$2.7

PharmacyChecker.com

TIME, FEBRUARY 2, 2004

Further enclosures are attached with articles.